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Date April 23, 2002

By:

Carol A. See
Carol A. See



PATENT
Docket No. GCX329-US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of)	
)	
Van der Laan et al.)	Group Art Unit: 1652
)	
Serial No. 07/565,673)	Examiner: Christian Fronda
)	
Filed: August 10, 1990)	Appeal No.:
)	
For: Efficient Production of Mutant Proteases))	

APPELLANTS' BRIEF ON APPEAL

Box AF
Commissioner for Patents
Washington, D.C. 20231

Sir:

Pursuant to 37 C.F.R. §§1.191 - 1.192, Appellants file this Brief in support of the Notice of Appeal, dated January 23, 2002. A petition, requesting a one-month extension of time, to file said Brief is concurrently submitted herewith. Appellants respectfully submit, in view of the facts, arguments and authorities set forth below, the Board should find the final rejection of pending claims 41 - 55 to be in error and should reverse.

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1. REAL PARTY IN INTEREST

Pursuant to 37 C.F.R. §1.192(c)(1), Appellants J. C. van der Laan, et al. identify Genencor International, Inc. as the real party in interest in this appeal.

2. STATEMENT OF RELATED CASES

Pursuant to 37 C.F.R. §1.192(c)(2), counsel for Appellants state that this appeal was never previously before the Board of Patent Appeals and Interferences for final hearing.¹ There are no presently pending related appeals or interferences, or appeals which were decided by the Board, the Court of Appeals for the Federal Circuit, or a district court under 35 U.S.C. §146.

3. STATUS OF THE CLAIMS

The above-identified application has had a long history of prosecution and claim amendments. The presently appealed claims were principally introduced into prosecution upon the filing of a second submission under 37 C.F.R. §1.129(a) dated December 23, 1998. (See Appendix II.) Appellants have outlined the history of the claim amendments below.

The application was filed on August 10, 1990 with 21 original claims. A preliminary amendment dated September 23, 1991 cancelled claim 1 and added new claim 22. Amendments were made to claims 2, 3, 4, 5, 6, 7, 8, 9, 10 and 11.

In the response submitted April 24, 1992, claims 2, 3 and 18 were canceled and claims 4, 5, 6, 7, 9, 10, 12, 14, 15, 17 and 19 were amended. Further, claims 20 - 22 were cancelled and essentially rewritten as new claims 23 - 26.

1. An Appeal Brief dated March 2, 1994 was filed with the Board of Appeals and Interferences. A copy of the claims is appended hereto as Appendix III. The issues on appeal concerned rejections under 35 U.S.C. §112 and 35 U.S.C. §103. However, the appeal was never considered by the Board, and prosecution of the application was reopened. A copy of the Appeal Brief will be submitted if requested by the Examiner or the Board.

A further amendment was submitted December 15, 1992, wherein claims 6, 7, 10, 11, 12, 14, 17, 23 and 26 were amended. In response to a final office action dated March 2, 1993, claims 9, 14, 17, 19, 23, 24, 25, and 26 were amended and concurrently a notice of appeal was filed. An advisory action dated September 27, 1993 indicated the amendment filed in response to the final rejection would not be entered and the claims remained rejected.

An appeal brief was filed March 2, 1994. For the Board's convenience a copy of the appealed claims is appended hereto as Appendix III.

In response to the appeal, Appellants received a further non-final action. In reply, claim 17 was cancelled; claims 12, 14, 15, 19, 23, 24, 25 and 26 were amended; and claims 27 - 29 were added.

On July 7, 1995, in response to a final office action dated Feb 14, 1995, Appellants cancelled claim 16 and amended claims 9, 12, 19, 23, 24, 25, 26 and 27. The amendment was entered, but the claims remained rejected. A notice of appeal was filed.

Subsequently, on October 16, 1995, a response was filed under 37 C.F.R. §1.129(a). A preliminary amendment filed November 28, 1995 added new claims 30 - 33. A further amendment dated April 17, 1996 was filed, wherein claims 4, 13, 14, 19, 23, 24, 25, 26, 28, 29, 30 and 33 were amended and claims 34 - 37 were added. A non-final office action dated September 4, 1996 again rejected pending claims 4 - 7, 9 - 15, 19, and 23 - 37. In response, claims 11, 15, 26 - 28 and 36 - 37 were canceled; claims 4, 5, 6, 7, 9, 10, 12, 13, 14, 23, 29, 30, 34 and 35 were amended and claims 38 - 40 were added. A final rejection dated April 1, 1997 was received, and Appellants filed a notice of appeal on Oct. 1, 1997 appealing claims 7, 9 - 10, 12 - 14, 19, 23 - 25, 29 - 35 and 38 - 40.

However, Appellants did not file an Appeal Brief. When a new representative for Appellants reviewed the file, it was discovered that the application was actually abandoned due to filing the October 16, 1995, 37 C.F.R. §1.129(a) submission subsequent to filing the March 1994 Appeal Brief. On December 23, 1998, Appellants filed a timely petition to revive the unintentionally abandoned application and to accept the first submission made under 37 C.F.R. §1.129(a). Additionally, Appellants filed a second submission under 37 C.F.R. §1.129(a) which included an amendment canceling

the pending claims, 4 - 7, 9 - 10, 12 - 14, 19, 23 - 25, 29 - 35 and 38 - 40 and submitting new claims 41 - 53. A copy of claims 41 - 53 has been appended hereto as Appendix II. Appellants were notified in a communication from the Petitioner's Office dated August 9, 1999 that (i) the petition to revive the abandoned application was granted; (ii) the rules were waived with respect to the first submission under 37 C.F.R. §1.129(a) and said submission was accepted; and (iii) the second submission under 37 C.F.R. §1.129(a) was accepted.

In response to an office action dated June 27, 2000, claims 44, 49 and 51 were amended. A further amendment was filed July 24, 2001, wherein claims 41, 45, 47, 48 and 50 were amended and claims 54 and 55 were added. It is the rejection of these claims, claims 41 - 55, that are contested in the instant Brief on Appeal. A copy of the pending rejected claims is attached hereto as Appendix I.

4. STATUS OF THE AMENDMENTS

There have been no further amendments submitted in response to the final rejection dated October 23, 2001.

5. SUMMARY OF THE INVENTION

The claimed invention is directed to methods for preparation of mutant high alkaline *Bacillus* proteases using alkalophilic *Bacillus* host strains that have been modified to lack the capacity to produce the corresponding wild-type protease and also modified to produce a mutant high alkaline protease. (Specification, page 4, lines 14 - 26; page 6, lines 17 - 26 and page 10, lines 11 - 20).

Preferably, the alkalophilic *Bacillus* host strain has been modified by chromosomal deletion of a gene encoding the wild-type protease (Specification, page 7, lines 28 - 38). Additionally, the mutant high alkaline protease is preferably introduced into the host strain by an integration cassette comprising a DNA sequence encoding the mutant protease. (Specification, page 8, lines 1 - 4). Preferably, the mutation of the host *Bacillus* strain is a non-reverting mutation (Specification, page 7, lines 16 - 17).

In a specific embodiment, the method comprises the production of a mutant high alkaline protease in *Bacillus novo* species PB92 and derivatives thereof wherein the derivative retains the characteristics of *B. novo* species PB92 and *B. novo* species PB92 or a derivative thereof has been modified to lack the capacity to produce wild-type protease. (Specification, page 12, lines 8 - 21).

6. STATEMENT OF THE ISSUES FOR REVIEW

The final rejection presents four issues for review.

1. Whether claims 41 – 47 are unpatentable under 35 U.S.C. §112, second paragraph as being indefinite.
2. Whether claims 54 and 55 are unpatentable under 35 U.S.C. §112, second paragraph as being indefinite.
3. Whether claims 41 - 55 are unpatentable under 35 U.S.C. §112, first paragraph as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.
4. Whether claims 41 - 55 are unpatentable under 35 U.S.C. §112, first paragraph as being non-enabled.

7. GROUPING OF CLAIMS

Appellants maintain that rejected claims 41 – 55 do not stand and fall together. The claims are grouped and argued as follows:

- A. Claims 41 - 53 which are grouped and argued together, and
- B. Claims 54 and 55 which are grouped and argued together.

Reasons as to why Appellants consider the rejected claims to be separately patentable are presented in paragraph (8) below.

8. ARGUMENT

In order to further facilitate an understanding of the instant invention, Appellants reiterate that the present invention solves a significant problem in the area of heterologous protease production in *Bacillus* strains and particularly in industrial *Bacillus* strains. As taught in the specification at pages 1 and 2, *Bacilli* are widely used for the production of industrially important enzymes including proteases. However, production host *Bacillus* strains produce proteolytic activity, and about 90% of this proteolytic activity is attributed to wild-type indigenous proteases. These proteases tend to degrade heterologous proteins that are produced by the *Bacillus* strains. The present invention solves this problem such that high alkaline proteases may be produced in *Bacillus* strains wherein the *Bacillus* strains are essentially devoid of indigenous alkaline proteases.

1. Claims 41 – 47 are not indefinite under 35 U.S.C. §112, second paragraph even though the specific amino acid residues in the claimed "mutant high alkaline protease" are not specifically defined.

The second paragraph of section 112, requires that an applicant must claim their invention with precision and definiteness by clearly setting out the boundaries of the subject matter for which protection is granted. Definiteness of claim language must be analyzed in light of (1) the content of the disclosure, 2) the teachings of the prior art and 3) the claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made.

The Examiner has stated, "because it is not known what specific amino acid residue(s) in the claimed "mutant high alkaline protease" are to be mutated and one of skill in the art cannot determine the metes and bounds of the claimed invention", independent claim 41 and those dependent thereon are indefinite.

Appellants believe the reasoning for this rejection is erroneous. The fact that the specification does not explicitly delineate the precise amino acid residues that must be

mutated does not necessarily make the phrase "mutant high alkaline protease" indefinite. Appellants contend the phrase is clear and definite.

High alkaline proteases are defined at page 10, lines 11 – 20 of the specification as proteases produced by alkalophilic *Bacillus* strains. An alkalophilic *Bacillus* strain, according to the invention, is defined as a strain that grows under alkaline conditions, generally pH 9 – 11. The specification specifically references Horikoshi and Akiba (1982) "Alkalophilic Microorganisms" Springer Verlag, N.Y. and cites USP 3,723,250, USP 4,489,037 and RE 30,602 as sources for examples of *Bacillus* strains capable of growing at alkaline pH's. Therefore, a high alkaline protease is a protease obtained from an alkalophilic *Bacillus* strain. At the time of filing the instant specification numerous protease sequences were known.

At page 13, lines 1 - 2 of the specification it is stated,

.." most preferably the mutant protease is one described in EP-A-0328229 and WO 89/06279 and capable of production on an industrial scale." .

and at lines 8 - 15,

"Where it is desired to obtain a mutated protease, the DNA sequence can be mutated so that at least one amino acid is different from the wild type protease. More than one amino acid may be mutated so long as the resulting peptide maintains the capacity to degrade. In some instances the reaction rate may be lower than that of the native protease; or it may be the same or greater reaction rate as native protease, depending upon the desired application."

Appellants submit that one of skill in the art would have an immediate understanding of the phrase "mutated high alkaline protease" from the teachings of the specification and the content of the prior art.

The USPTO has also gone on record as stating that preparing mutants of known proteases would be well within the ordinary skill in the art and not require undue experimentation. See the Office Action mailed September 24, 1991, page 8, lines 23-25 and page 9, line 1. A copy of which is appended herein as Appendix IV. Additionally, Appellants teach the protease gene may be modified by site-directed mutagenesis (Specification, page 9, lines 19 - 22 and example 3 at page 21 et seq.).

2. The phrases "*Bacillus novo* species PB92 and its derivatives" and "*Bacillus novo* species PB92 or derivative thereof" do not render claims 54 and 55 indefinite under 35 U.S.C. §112, second paragraph.

The same rules of law apply to instant argument 2 as presented above for argument 1, and are therefore not repeated herein.

The absence of a specific definition of a *Bacillus novo* species PB92 derivative and the absence of a list of derivatives does not render the term indefinite. One of ordinary skill in the art is well aware of and can obtain host cells of *Bacillus novo* species PB92. As taught in Appellants' specification, *Bacillus novo* species PB92 is disclosed *inter alia* in U.S. Patent No. RE 30,602. RE 30,602 teaches a culture of the *B. novo* species PB92 strain was deposited with the Laboratory for Microbiology of the Technical University at Delft, the Netherlands and given number Or-10. In the instant specification, the term "derivative" is given its common meaning. As defined in the Oxford American Dictionary (1980), derivative means - (n) a thing that is derived from another. In this specific case the derivative is derived from *B. novo* species PB92. (See, Appendix V).

Additionally, at page 12 of the instant disclosure Appellants teach,

"An example of an alkalophilic *Bacillus* host strain is *Bacillus novo* species PB92 disclosed *inter alia* in U.S. Patent No. RE 30,602. Derivatives of these alkalophilic *Bacillus* strains, that have been optimized for protease production, are employed to produce their proteases on an industrial scale (see EP-A-0284126)."

Moreover, derivatives of *Bacillus novo* species PB92 are further defined in the claims as retaining the characteristics of *Bacillus novo* species PB92. This recital sets definite boundaries on the patent protection sought.

3. The subject matter as claimed in claims 41 - 55 was described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

a) Adequate written description support is found in the specification for claims 41 - 53.

The Examiner has alleged the Appellants were nonresponsive to the written description rejection as presented in the office action dated March 29, 2001 (paper no. 61). In the March 29, 2001 office action the Examiner stated,

"Claims 41, 49 and 50 are directed toward a gene encoding all possible "mutant high alkaline" proteases and all possible "wild-type high alkaline" proteases. The specification, however, only provides the following representative species of mutant alkaline protease encompassed by these claims: gene encoding a mutant alkaline protease comprising a nucleotide sequence consisting of the gene encoding the wild-type protease of *Bacillus novo* species PB92 having the codon for M216 replaced with a codon coding for Q, the codon for S160 replaced with a codon coding for D, or the codon of N212 replaced with a codon coding for *Bacillus novo* species PB92 as the single representative species of the claimed "wild-type high alkaline" proteases. There is no disclosure of any particular structure to function/activity relationship in the disclosed species. The specification also fails to describe additional representative species of these "mutant high alkaline" proteases or "wild-type alkaline" proteases by any identifying structural characteristics or properties for which no predictability of structure is apparent. Given this lack of additional representative species as encompassed by the claims, Applicants have failed to sufficiently describe the claimed invention, in such clear concise and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention."

While the Examiner has referred to claims 41, 49 and 50, Appellants realize it is claims 41, 48 and 50, the independent claims, that the Examiner meant to reference.

At the onset, Appellants again emphasize the invention concerns a broad method for preparing mutant proteases in a modified *Bacillus* host wherein the modified *Bacillus* host lacks the capacity (or has a reduced capacity) to produce a corresponding native protease. (See claims 41 and 48 and those dependent thereon). The nexus of the invention is the modification of a *Bacillus* host to reduce its capacity to produce unwanted proteases which tend to degrade heterologous proteins produced by the host strain (Specification pages 1 and 2).

The function of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application relied on, of the specific subject

matter later claimed by him. To comply with the description requirement, it is not necessary that the application describe the claimed invention in *ipsis verbis*, all that is required is that it reasonably convey to a person skilled in the art that as of the filing date thereof, the inventor had possession of the subject matter later claimed. *In re Edwards*, 196 USPQ 465 (CCPA 1978) and *In re Wertheim*, 191 USPQ 90 (CCPA 1976).

The claims are directed to mutant non-reverting alkalophilic *Bacillus* strains, and while the examples are specifically directed to *Bacillus* novo species PB92 and derivatives thereof, it is asserted the written description in the specification supports the broader claims. Various *Bacillus* strains are mentioned in the application which may be used as hosts and reference is made to page 10, lines 21 - 32, page 11, lines 3 - 21 and page 12, lines 8 - 21. As stated at page 10, lines 29 - 32, "Examples of *Bacillus* strains capable of growing at alkaline pH are described in, for example, U.S. Patent Nos. 3,723,250, RE. 30,602 and 4,480,037."

While Appellants did not explicitly list various *Bacillus* host strains, one of general skill in the art at the time the application was filed would know of various *Bacillus* strains including *B. licheniformis*, *B. subtilis*, *B. lentus*, and *B. amyloliquefaciens* which could be used as host strains. Each of these species are mentioned in the specification. For example, *B. subtilis* is mentioned at page 3, lines 1 - 11; *B. lentus*, is mentioned at page 12, lines 16 - 21; *B. amyloliquefaciens* is mentioned at page 3, lines 24 - 29, page 4, lines 1 - 4 and *B. licheniformis* is mentioned at page 4, lines 6 - 9.

The Examiner also contends the structure of the wild-type high alkaline proteases are not disclosed and the sequences for mutant high alkaline proteases are not disclosed, and therefore the specification fails to provide adequate written description. However, Appellants contend that it is not necessary to describe the sequence of numerous wild-type proteases or mutant proteases. One reading the specification would clearly understand that a wild-type protease could easily be obtained from an alkalophilic *Bacillus* host and once a *Bacillus* host was modified by deletion of the gene encoding the wild-type protease, one skilled in the art could transform the *Bacillus* with an integration cassette comprising a gene encoding a heterologous protease. While the specification does not explicitly list numerous mutant proteases that could be incorporated into an integration cassette, the specification recites US patents

wherein numerous mutant proteases are taught. There is no requirement under section 112, that the subject matter of a claim be described literally in the disclosure. To satisfy the written description requirement, the applicant must convey with reasonable clarity to those of ordinary skill in the art that, as of the filing date sought, he had possession of the invention. In demonstrating that the requirement is satisfied, an applicant is not limited to the specification. See, for example, *Martin v. Mayer* 3 USPQ2d 1333 (Fed. Cir. 1987).

b) Adequate written description support is found in the specification for claims 54 - 55.

With respect to the alleged failure to provide an adequate written description of claims 54 - 55 the Examiner has stated,

"The claims are directed toward a gene encoding all possible "mutant high alkaline" proteases, all possible "derivatives" of *Bacillus novo* species PB92, all host cells incapable of producing a "wild-type high alkaline" proteases (sic). The specification, however, only provides the following representative species of mutant alkaline proteases encompassed by these claims: a gene encoding a mutant alkaline protease comprising a nucleotide sequence consisting of the gene encoding the wild-type alkaline protease of *Bacillus novo* species PB92 having the codon for M216 replaced with a codon coding for Q, the codon for S160 replaced with the codon coding for D, or the codon of N212 replaced with a codon coding for D. The specification only teaches the wild-type alkaline protease of *Bacillus novo* species PB92 as the single representative species of the claimed "wild-type high alkaline" proteases. The specification only discloses *Bacillus novo* species PB92 as the *Bacillus* host. There is no disclosure of any particular structure to function/activity relationship in the disclosed species of the wild-type protease of *Bacillus novo* species PB92 or the gene encoding the wild-type alkaline protease of *Bacillus novo* species PB92 having the codon for M216 replaced with the codon coding for Q, the codon for S160 replaced with a codon coding for D, or the codon of N212 replaced with a codon coding for D. Furthermore, there is no written description of any "derivative" of *Bacillus novo* species PB92."

As stated above and repeated herein, the function of the written description requirement is to ensure that the inventor had possession, as of the filing date of the

application relied on, of the specific subject matter later claimed by him. To comply with the description requirement, it is not necessary that the application describe the claimed invention in *ipsis verbis*, all that is required is that it reasonably convey to a person skilled in the art that as of the filing date thereof, the inventor had possession of the subject matter later claimed. *In re Edwards*, 196 USPQ 465 (CCPA 1978) and *In re Wertheim*, 191 USPQ 90 (CCPA 1976).

Claims 54 and 55 are directed to a method for the production of a mutant high alkaline protease from a *Bacillus novo* species PB92 or derivative thereof as a host cell wherein the host cell has been modified by chromosomal deletion of the gene encoding the wild-type protease. As argued above under Argument 8(1) and 8(2) the terms "*Bacillus novo* species PB92 derivative" and "mutant high alkaline protease(s)" are not vague but definite.

In the specific examples, Appellants disclose a derivative of *Bacillus novo* species PB92, that is *Bacillus* strain PBT110. Further derivatives are disclosed as *Bacillus* PBT125 and PBT 126 and reference is made to example 2, page 16; example 4, page 23 and Table 1, page 29.

As acknowledged by the Examiner specific examples in the specification disclose specific mutant proteases (page 23, lines 19 - 23) in strains PEP111 and PEP112 (page 26, lines 33 - 36 and page 27, lines 1 - 3). However, Appellants should not be limited to these specific derivatives or mutant proteases. A preferred group of mutant proteases is disclosed at the bottom of page 12 and bridging page 13 of the specification. It is stated "Preferably the polypeptide is a mutant high alkaline protease, most preferably the mutant protease is one described in EPA 0328229 and WO89/06279 and capable of production on an industrial scale."

For example, with respect to EPA 0328229², it is taught that preferred mutations of PB92 protease include positions 60, 94, 97, 102, 105, 116, 123 - 128, 150, 152, 153, 160, 183, 203, 211, 212, 213, 214, and 216. Particularly preferred positions are disclosed as positions 116, 126, 127, 128, 160, 166, 169, 212, and 216.

2. Appellants have not provided a copy of EPA-0328229 but will expeditiously provide a copy if requested by the Examiner or the Board.

At page 23, lines 19 - 23 of the instant specification with reference to the construction of vectors for industrial protease production, it is explicitly stated: "This procedure is illustrated in Figure 11 using as (sic) example the use of mutation M216Q to construct in plasmid pBHB-MXL M216Q. M216Q, and also M216S, S160D and N212D referred to hereinafter, are mutant proteases of *Bacillus* PB92, and described in EP-A-0328229."

Claims 54 and 55 are directed to the replacement of at least one amino acid residue in the nucleotide sequence encoding the wild-type protease of *Bacillus* novo species PB92 or a derivative thereof. While Appellants specifically made mutations at positions 160, 212 and 216 of *Bacillus* novo species PB92, Appellants assert the written description supports various mutations of the wild type PB92 protease. It is further asserted it is not whether the description is literally in the specification with respect to the numerous possible mutations in the PB92 protease gene or with respect to the numerous possible PB92 derivatives, but what is conveyed to one having ordinary skill in the art reading the specification. (*In re Smythe*, 178 USPQ 279 (CCPA 1973)).

4. The specification is enabling for a wild-type alkaline protease of a *Bacillus* species broader than the wild-type alkaline protease of *Bacillus* novo species PB92 as claimed in claims 41 - 55.

a) Enablement of Claims 54 - 55.

Claims 54 and 55 are narrower than claims 41 - 53 and are addressed first. These claims are directed to a host which is a *Bacillus* novo species PB92 or a derivative thereof which is incapable of producing a wild-type high alkaline protease due to a chromosomal deletion of the gene encoding the wild-type protease, and wherein the *Bacillus* host is transformed with a cassette comprising a gene encoding a mutant high alkaline protease which comprises a replacement of at least one amino acid residue in the sequence encoding the wild-type protease.

As held in *Ex parte Goeddel*, mere broad generalizations and allegations are insufficient for a holding of non-enablement. As stated, the ultimate question in each case manifestly is whether or not it contains sufficiently explicit disclosure enabling the average routineer in the field to practice an invention claimed therein. (*In re Goeddel*, 5

USPQ2d 1449 (Bd. Pat. App. & Int'f 1987). Moreover, compliance with the enablement requirement is not precluded even if some experimentation is necessary, although the amount of experimentation may not be unduly extensive (*Hybritech Inc., v. Monoclonal Antibodies, Inc.* 231 USPQ 81 (Fed. Cir. 1986))

In spite of the explicit teachings provided by the specification and the knowledge available to the skilled artisan at the effective priority date of the present invention, the Examiner alleges that the present specification is enabling *only* for claims limited to the illustrative examples, i.e., methods of producing an alkalophilic *Bacillus novo* species PB92 of minimal indigenous extracellular protease level, transformed with a mutated *B. novo* PB92 alkaline protease described in the specification. Appellants believe that the claims should not be limited only to embodiments described in the illustrative examples.

Appellants assert that they have taught how to make and use the presently claimed invention and that no undue experimentation would be required to practice it. It is well established that a patent need not disclose what is well known in the art and thus available to the public. Appellants submit that *Bacillus novo* species PB92 and derivatives thereof were known in the art and fully enabled by the instant specification. The Board's attention is directed to page 12, lines 8 - 14; page 16, line 32 which discloses PBT110, a PB92 derivative; and page 18, lines 9-14, which discloses PBT 125 and PBT 126 both protease negative, asporogenic strains.

Mutant high alkaline proteases from PB92 were also known in the art and referenced in the specification at page 12, lines 17 - 21 and page 13, lines 1 - 2. Tools necessary for mutating, cloning and transforming genes were known or well within the skill of those in the art as of the effective priority date of the present invention and are further described at pages 13 - 15.

b) Enablement of Claims 41 - 53.

The Examiner has stated at page 3 of the final rejection,

".. while being enabling for the wild-type alkaline protease of *Bacillus novo* species PB92, the gene encoding said wild-type alkaline protease of *Bacillus novo* species PB92, and a gene encoding a mutant alkaline protease comprising a nucleotide sequence consisting of the gene encoding the wild-type alkaline protease of *Bacillus novo* species PB92 having the codon for M216

replaced with a codon coding for Q, the codon for S160 replaced by the codon coding for D, or the codon of N212 replaced with the codon coding for D; does not reasonably provide enablement for any wild-type alkaline protease or any gene encoding any mutant alkaline protease."

Further the Examiner asserts at page 4 of the final rejection,

"The amount of experimentation to practice the claimed invention is enormous and entails screening a vast number of organisms for an organism containing a wild-type alkaline protease, selecting and isolating a wild-type protease from the selected biological source, obtaining the amino acid sequence of the isolated wild-type protease, obtaining the gene encoding the isolated wild-type protease from libraries constructed from the selected biological source and recombinantly expressing the wild-type protease using the gene encoding the wild-type protease. Furthermore, such experimentation entails selecting a wild-type alkaline protease to mutate, selecting a mutation to perform on the amino acid sequence of the wild-type alkaline protease such as substitution, addition, deletion, or combinations thereof of amino acid residues, obtaining the gene encoding the selected wild-type alkaline protease, mutate the gene encoding the wild-type protease, express the mutant alkaline protease and screening for mutants that still have alkaline protease activity."

Appellants assert that claims need not be limited to illustrative examples or preferred embodiments in order to satisfy enablement requirements. The CCPA emphasized that: "To demand that [Applicant] shall limit his claims . . . to materials which meet the guidelines specified for "preferred" materials in a process . . . would not serve the constitutional purpose of promoting progress in the useful arts." (*In re Goffe*, 191 USPQ 429, 431 (CCPA 1976)). Additionally, as held by the courts in *Texas Instr. Inc. v United States ITC* (231 USPQ 833, Fed. Cir. 1986) compliance with Section 112, first paragraph does not require that an applicant describe in the specification every conceivable and possible future embodiment of his invention.

Appellants have discovered an answer to an important problem, that is if one deletes the wild-type gene which encodes a high alkaline protease in an alkalophilic *Bacillus* the production and secretion of the wild-type protease which results in proteolytic degradative activity will be reduced and one can then transform the alkalophilic *Bacillus* with DNA encoding a heterologous protease. Appellants specifically

use *Bacillus* novo species PB92 and a few derivatives thereof in the illustrative examples, but as repeated numerous times in the specification other *Bacillus* species may be used, and it would be industrial *Bacillus* species wherein the invention would have its most significance (Specification, page 10). To limit Appellants' invention to only *Bacillus* novo species PB92 would inherently be unfair. Others could take the teachings of the present specification and merely use the teachings to produce a *Bacillus* species other than *Bacillus* novo species PB92 having a deletion in the chromosome encoding the wild-type protease.

The Examiner has also alleged the claims are not enabled for claims to "mutant high alkaline protease". However, Appellants assert knowing the type of mutation induced in a particular protease gene or even the effect of a mutation on protease function is not required in order to practice the invention. There is no recitation that the mutations have a higher, lower or equivalent reaction rate as the wild-type protease. (Specification, page 13, lines 8 -16). The presently claimed invention only requires that the host cell will produce the mutant protease.

The point of the invention is that any mutant protease can be produced more readily in a *Bacillus* strain which has a reduced indigenous protease level due to deletion of an indigenous protease gene. Not only were numerous proteases known at the time of the invention, but several methods of producing mutant proteases differing in at least one amino acid were well known in the art. The specification teaches;

1) high alkaline protease genes and wild-type alkaline protease genes at page 10, lines 21-32; page 12, lines 8-21; and in example 3;

2) mutant proteases at page 13, lines 1-16; and mutation of a protease gene in example 3;

3) cloning and transformation techniques at page 9, lines 26-38 through page 10, lines 1-2; page 13, lines 17-38; page 14, lines 1-38; and in particular, transformation techniques for alkalophilic *Bacillus* strains are disclosed at page 14, lines 23-25; and

4) production of non-reverting alkalophilic *Bacillus* strain hosts at page 7, lines 17- 38 through page 9, lines 1-26; page 10, lines 3-10; and page 12, lines 31-33.

It is also respectfully submitted that the USPTO has gone on record as stating that preparing mutants of known proteases would be well within the ordinary skill in the

art and not require undue experimentation. (Office Action mailed September 24, 1991, page 8, lines 23-25 and page 9, line 1 and attached hereto as Appendix IV).

It is well established law that to be enabling, the specification need only provide sufficient information to allow one skilled in the art to make and use the invention without undue experimentation. *Scripps Clinic & Research Found. V. Genentech, Inc.*, 927 F.2d 1565, 18 USPQ 2d 1001, 1006 (Fed. Cir. 1991). Appellants believe that they have provided sufficient information to teach one of skill in the art how to make and use the invention and that no undue experimentation would be required to practice it.

Appellants submit that requiring disclosure of all possible embodiments of an invention *is not* an appropriate test for enablement under *In re Wands* (8 USPQ2d 1400 (Fed. Cir. 1988)). As mentioned above, the specific nucleic acid sequence of the high alkaline protease is irrelevant to the claimed invention, and as held by the courts in *Texas Instr. Inc. v United States ITC* (231 USPQ 833, Fed. Cir. 1986) compliance with Section 112, first paragraph does not require that an applicant describe in the specification every conceivable and possible future embodiment of his invention.

Applicants assert that they have taught how to make and use the presently claimed invention and that no undue experimentation would be required to practice it.

The presently claimed invention provides that mutant high alkaline protease can be produced in a recombinant *Bacillus* host and in the absence of contamination with wild type protease by using as a host strain an alkalophilic *Bacillus* strain that is incapable of producing its wild-type protease and wherein the strain is incapable of reverting back to the wild-type genotype. The presently claimed invention is directed to methods for the production of mutant high alkaline protease, methods of obtaining non-reverting alkalophilic *Bacillus* strains and alkalophilic *Bacillus* strains for use in the methods.

9. SUMMARY

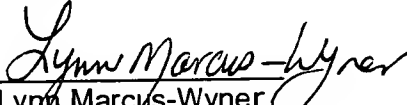
In conclusion, Appellants believe the claimed invention meets all requirements under 35 U.S.C. §§ 112 first and second paragraphs. Further Appellants contend that the issues concerning group A claims (41 - 53) are related but different from the issues concerning group B claims (54 - 55), and each group of claims is separately patentable.

As prescribed by 37 CFR §1.192(c)(7), the claims on appeal are found in the attached Appendix I.

As prescribed by 37 CFR §1.192(a), this Brief on Appeal is submitted in triplicate.

An early decision on the merits is kindly solicited.

Respectfully submitted,


Lynn Marcus-Wyner
Registration No. 34,869

Date: April 23, 2002

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APPENDIX 1

APPENDIX I - PENDING CLAIMS 41 - 55 ON APPEAL

41. (Once amended) A method for the production of a mutant high alkaline protease, said method comprising the steps of:

a) obtaining a non-reverting mutant alkalophilic *Bacillus* host incapable of producing a wild-type high alkaline protease, wherein said mutant alkalophilic *Bacillus* host comprises a chromosomal deletion of the gene encoding the wild-type alkaline protease and an integration cassette comprising a gene encoding a mutant high alkaline protease; and

b) growing said mutant alkalophilic *Bacillus* host under conditions whereby said mutant high alkaline protease is expressed.

42. (Reiterated) The method of Claim 41 further comprising the step of isolating said mutant high alkaline protease.

43. (Reiterated) The method of claim 41 wherein said alkalophilic *Bacillus* host is an asporogenic alkalophilic *Bacillus* strain.

44. (Once amended) The method of Claim 41 wherein said alkalophilic *Bacillus* strain is *Bacillus novo* species PB92 or the derivative PBT 110.

45. (Once amended) The method of Claim 41 wherein said gene encoding the wild-type alkaline protease in said mutant alkalophilic *Bacillus* host has been deleted by homologous or illegitimate recombination.

46. (Reiterated) The method of Claim 41 wherein said integration cassette is contained in a plasmid.

47. (Once amended) The method of Claim 41 wherein said integration cassette is integrated into the genome of said mutant alkalophilic *Bacillus* host.

48. (Once amended) A method of obtaining a non-reverting mutant alkalophilic *Bacillus* strain having a reduced level of a wild-type high alkaline protease, said method comprising the steps of:

- a) transforming an alkalophilic *Bacillus* strain comprising a gene encoding the wild-type alkaline protease with a cloning vector comprising DNA encoding a replication function and 5' and 3' flanking non-coding regions of said gene encoding the wild-type high alkaline protease but not the coding region of said gene encoding the wild-type high alkaline protease gene, wherein a sufficient amount of said 5' and 3' flanking non-coding regions is present to provide for homologous recombination with the indigenous gene encoding the wild-type alkaline protease of said alkalophilic *Bacillus* strain whereby transformants having a reduced level of said wild-type alkaline protease are obtained;
- b) growing said transformants under conditions whereby the replication function encoded by said cloning vector is inactivated; and
- and
- c) isolating transformants having a reduced level of the wild-type alkaline protease.

49. (Once amended) The method of Claim 48 wherein said alkalophilic *Bacillus* strain is *Bacillus novo* species PB92 or the derivative PBT 110.

50. (Once amended) A mutant alkalophilic *Bacillus* strain producing a mutant high alkaline protease and no detectable level of a wild-type high alkaline protease, wherein said mutant alkalophilic *Bacillus* strain is obtained by growing an alkalophilic *Bacillus* strain which is incapable of producing said wild-type high alkaline protease transformed with a plasmid expression vector comprising said mutant high alkaline protease gene.

51. (Once amended) The alkalophilic *Bacillus* strain of Claim 50 wherein said strain is *Bacillus novo* species PB92 or the derivative PBT110.

52. (Reiterated) The alkalophilic *Bacillus* strain of Claim 50 wherein said strain is a non-reverting strain.

53. (Reiterated) The alkalophilic Bacillus strain of Claim 50 wherein said strain is asporogenic.

54. (Reiterated) A method for the production of a mutant high alkaline protease, said method comprising the steps of:

a) obtaining an alkalophilic Bacillus host selected from the group consisting of Bacillus novo species PB92 and its derivatives wherein said derivatives retain the characteristics of Bacillus novo species PB92 and said alkalophilic Bacillus host is incapable of producing a wild-type high alkaline protease, and comprises a chromosomal deletion of the gene encoding an the wild-type high alkaline protease;

b) transforming said alkalophilic Bacillus host with an integration cassette comprising a gene encoding a mutant high alkaline protease, wherein said gene encoding the mutant high alkaline protease comprises a replacement of at least one amino acid residue in the nucleotide sequence encoding the wild type protease of Bacillus novo species PB92 or derivative thereof to obtain a non-reverting mutant alkalophilic strain; and

c) growing said mutant alkalophilic Bacillus host under conditions whereby said mutant high alkaline protease is expressed.

55. (Reiterated) The method according to claim 54 wherein the replacement is at an amino acid residue position selected from the group consisting of positions of 160, 216 and 212.

APPENDIX II

APPENDIX II - CLAIMS SUBMITTED IN THE SUBMISSION UNDER 37 CFR 1.129(a)

41. A method for the production of a mutant high alkaline protease, said method comprising the steps of:
- a) obtaining a non-reverting alkalophilic *Bacillus* host incapable of producing a wild-type high alkaline protease, wherein said *Bacillus* host comprises an integration cassette comprising a gene encoding said mutant high alkaline protease; and
 - b) growing said *Bacillus* host under conditions whereby said mutant high alkaline protease is expressed.
42. The method of Claim 41 further comprising the step of isolating said mutant high alkaline protease.
43. The method of Claim 41 wherein said alkalophilic *Bacillus* host is an asporogenic alkalophilic *Bacillus* strain.
44. The method of Claim 41 wherein said alkalophilic *Bacillus* strain is a *Bacillus* *novo* species PB92 or a derivative thereof said derivative retaining characteristics of the parent strain.
45. The method of Claim 41 wherein said wild-type protease gene has been deleted by homologous or illegitimate recombination.
46. The method of Claim 41 wherein said integration cassette is contained in a plasmid.
47. The method of Claim 41 wherein said integration cassette is integrated into the genome of said alkalophilic *Bacillus* host.
48. A method of obtaining a non-reverting alkalophilic *Bacillus* strain having a reduced level of extracellular high alkaline protease, said method comprising the steps of:
- a) transforming an alkalophilic *Bacillus* strain comprising a wild-type high alkaline protease gene with a cloning vector comprising DNA encoding a

replication function and 5' and 3' flanking non-coding regions of said high alkaline protease gene but not the coding region of said high alkaline protease gene, wherein a sufficient amount of said 5' and 3' flanking non-coding regions is present to provide for homologous recombination with said wild-type high alkaline protease gene whereby transformants having a reduced level of high alkaline protease are obtained;

- b) growing said transformants under conditions whereby the replication function encoded by said cloning vector is inactivated; and isolating transformants having a reduced extracellular alkaline protease level.

- 49. The method of Claim 48 wherein said alkalophilic Bacillus strain is *Bacillus novo* species PB92 or a derivative thereof said derivative retaining characteristics of the parent strain.
- 50. An alkalophilic Bacillus strain producing a mutant high alkaline protease and no detectable wild-type extracellular high alkaline protease, wherein said Bacillus strain is obtained by growing an alkalophilic Bacillus strain which is incapable of producing said wild-type high alkaline protease transformed with a plasmid expression vector comprising said mutant high alkaline protease gene.
- 51. The alkalophilic Bacillus strain of Claim 50 wherein said strain is *Bacillus novo* species PB92 or a derivative thereof said derivative retaining characteristics of the parent strain.
- 52. The alkalophilic Bacillus strain of Claim 50 wherein said strain is a non-reverting strain.
- 53. The alkalophilic Bacillus strain of Claim 50 wherein said strain is asporogenic.

APPENDIX III - Claims in issue for Appeal Brief dated March 2, 1994

APPENDIX A- Claims as Pending

USSN 07/565,573

4. The method according to Claim 23, wherein said *Bacillus* strain is *Bacillus novo* species PB92 or a derivative thereof.

5. The method according to Claim 23, wherein said *Bacillus* strain is an asporogenic alkalophilic *Bacillus* strain.

6. The method according to Claim 23, wherein the gene encoding said indigenous protease has been deleted by homologous or illegitimate recombination.

7. The method according to Claim 23, wherein a plasmid comprises said expression cassette.

9. The method according to Claim 7, wherein said mutant high alkaline protease is obtained from *Bacillus novo* species PB92.

10. The method according to Claim 23, wherein at least one copy of said expression cassette is integrated into the genome of said host.

11. The method according to Claim 10, wherein said host further contains at least one copy of a plasmid comprising said expression cassette.

12. A method of obtaining an alkalophilic *Bacillus* strain having no detectable extracellular high alkaline protease, said method comprising:

transforming an alkalophilic *Bacillus* strain with a cloning vector comprising the 5' and the 3' flanking regions but not the coding region of a gene coding for the high alkaline protease and wherein a sufficient amount of said flanking regions is present to provide for homologous recombination with an indigenous gene coding for the high alkaline protease whereby transformants are obtained;

growing said transformants under conditions whereby the replication function encoded by said vector is inactivated; and

isolating transformants identified as having no detectable extracellular high alkaline protease.

13. The method according to Claim 12, wherein said alkalophilic *Bacillus* strain is *Bacillus novo* species PB92 or a derivative thereof.

14. An alkalophilic *Bacillus* strain producing a mutant high alkaline protease substantially free of expression product of an indigenous extracellular alkaline protease gene, wherein said strain has been obtained by transforming an alkalophilic *Bacillus* strain having no detectable indigenous extracellular high alkaline protease obtained by the method according to Claim 12 or 13 with a plasmid expression vector comprising the mutant high alkaline protease gene.

15. The *Bacillus* strain according to Claim 14, wherein said mutant alkalophilic *Bacillus* strain is a mutant of *Bacillus novo* species PB92 or a derivative thereof.

16. The *Bacillus* strain according to Claim 15, wherein said indigenous gene has been deleted by homologous or illegitimate recombination.

17. A mutant high alkaline protease produced according to the method of Claim 23 and characterized as (1) substantially free from contamination with an indigenous extracellular high alkaline protease, and (2) differing in at least one amino acid from the indigenous high alkaline protease.

19. A detergent composition comprising as an active ingredient one or more high alkaline protease prepared according to the method of Claim 23.

23. A method for production of a mutated high alkaline protease substantially free of indigenous extracellular high alkaline protease, said method comprising:

growing an alkalophilic *Bacillus* strain host having no detectable indigenous extracellular protease as a result of deletion of the gene for indigenous extracellular protease transformed with an expression cassette providing for expression of a said mutant high alkaline protease in said host, whereby said mutant high alkaline protease is produced.

24. A method for preparing a detergent composition, which comprises the step of combining a detergent composition with, as an active ingredient, one or more of a high alkaline protease prepared according to the method of Claim 23.

25. A method for processing laundry, which comprises the step of contacting said laundry with a detergent composition comprising as an active ingredient one or more of a high alkaline protease prepared according to the method of Claim 23.

26. A method for production of a mutated high alkaline protease substantially free of indigenous extracellular protease, said method comprising:

growing an asporogenous *Bacillus* strain host having a reduced indigenous extracellular protease level as a result of deletion of the gene for said indigenous extracellular protease transformed with an expression cassette providing for expression of a mutated high alkaline protease in said host, whereby said mutated high alkaline protease is produced.

APPENDIX IV -

Cover page and pages 8 & 9 of Office Action dated September 24, 1991



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Patent and Trademark Office

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SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
07/565,673	09/10/90	VAN DER LAAN	680-023

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RECEIVED

SEP 27 1991

COOLEY GODWARD CASTRO
HUDDLESON & TATUM

EXAMINER

HENDRICKS, K

ART UNIT	PAPER NUMBER
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184

DATE MAILED:

09/24/91

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☐ Responsive to communication filed on _____ ☐ This action is made final.
A shortened statutory period for response to this action is set to expire 3 month(s), _____ days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

- ☒ Notice of References Cited by Examiner, PTO-892.
- ☒ Notice re Patent Drawing, PTO-948.
- ☐ Notice of Art Cited by Applicant, PTO-1449.
- ☐ Notice of Informal Patent Application, Form PTO-152
- ☐ Information on How to Effect Drawing Changes, PTO-1474.
- ☐ _____

Part II SUMMARY OF ACTION

- ☒ Claims 1-21 are pending in the application.
Of the above, claims _____ are withdrawn from consideration.
- ☐ Claims _____ have been cancelled.
- ☐ Claims _____ are allowed.
- ☒ Claims 1-21 are rejected.
- ☐ Claims _____ are objected to.
- ☐ Claims _____ are subject to restriction or election requirement.
- ☒ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
- ☐ Formal drawings are required in response to this Office action.
- ☐ The corrected or substitute drawings have been received on _____ Under 37 C.F.R. 1.84 the drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
- ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____, has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
- ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
- ☐ Acknowledgement is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.

☐ This application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in

genes will generally inactivate the gene. Loss of expression of the gene can then be monitored and used for the selection of the desired recombinant strain. [pg. 9]" It is desirable to use a host cell with "reduced degradation of the desired product. [pg.13]" "The host cell can also be a mutant of an organism which produces the polypeptide of interest which itself, however, is a non-producer. Where the polypeptide of interest is a protease or an amylase, preferred strains include Bacillus novo species PB92...", etc.

Thus, it would have been obvious to one having ordinary skill in the art to combine the information provided by the two references in order to produce the claimed invention. Bott provides the general method for which to produce Bacillus strains incapable of producing certain desired proteases, wherein the transformation of these same hosts with a mutated "wild-type" protease gene results in the production of that single protease, essentially free of interfering proteases. Van Eekelen discloses the gene for Bacillus novo species PB92 high alkaline protease, and the use of this alkalophilic Bacillus host, with reduced degradation of the product, for the expression of these genes. Thus, it would have been obvious to use the detailed system of Bott et al. in a similar Bacillus species for the expression of a given, indigenous alkaline protease. The mutation of this protease, "differing in at least one amino acid from the wild-type protease", would also be within the ordinary skill in the

art, performed by similar methods disclosed by Bott et al.

Further, claims 17-21 are viewed as obvious over the prior art cited. The production of these particular mutated high alkaline proteases, substantially free from other proteases, is an inherent production resultant of the system of Bott et al. Also, these enzymes may be easily purified by methods common in the art, to insure their isolation from other alkaline proteases. Again, the use of the enzymes within detergent compositions in a laundry process has been shown by Bott et al.; and would be an obvious step to include. Thus, these claims are seen as obvious over the prior art cited, and are not deemed patentable.

Claims 12 and 14 are rejected under 35 U.S.C. § 102(b) as anticipated by or, in the alternative, under 35 U.S.C. § 103 as obvious over Fahnestock et al.

Fahnestock et al. disclose that "Bacillus strains having reduced levels of extracellular protease are produced by replacing the native chromosomal DNA sequence comprising the gene for an extracellular protease, such as subtilisin, with a partially homologous DNA sequence having an inactivating DNA segment inserted therein." The alkaline protease gene is inactivated by inserting a DNA fragment of chloramphenicol acetyltransferase (CAT) into the protease gene. Using homologous recombination, the original, functional gene is deleted. Also, the replication function of the cloning vector is inactivated,

APPENDIX V

Oxford American Dictionary

EUGENE EHRLICH
STUART BERG FLEXNER · GORTON CARRUTH
JOYCE M. HAWKINS

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Preface

This member of the Oxford family of dictionaries has been prepared especially for those who need a compact, up-to-date guide to American English. It contains words and phrases likely to be met in reading and everyday life, including many of slang, informal, and technical words and phrases. Names of states of the United States are included, as well as the capitals, terms used to designate the people of each state, and names of the provinces of Canada. Names of the peoples of the world, including those not yet well known, are given, as are names of the capital cities and the terms used to designate the people of each country.

We take this opportunity to express our gratitude to members of the Oxford Dictionary Department of the Oxford University Press for assistance of various kinds, particularly to John B. Sykes, Editor of the *Concise Oxford Dictionary*, 3rd edition, and to Dr. Robert Burchfield, Chief Editor of the Oxford English dictionaries. We are grateful as well to members of the staff of Oxford University Press in New York, particularly to Marjorie Mueller, Janice Lorimer, and John Carollo, for help in all stages of our work.

We wish also to express our gratitude to the many members of the Hudson Group dictionary staff who worked on the *American Dictionary*. In particular we wish to thank staff members: Ernest S. Hildebrand, Jr., Margaret Solomon, Felice Levy, Lawrence T. Lorimer, and Gloria Solomon; associate staff members: Pamela Dupuis, Mary Egner, Edward Ehrlich, Raymond V. Hand, Jr., Joan Lizzio, David Scott, and Katherine G. Scott; and assistant staff members: Jayne Ackerman, Christopher Carruth, Hayden Carruth,

-tohr-ee) *n.* (pl. *acc* for safekeeping) *hont* left his repository.

storehouse, especially. 2. a place for *units* and *replace* where goods are, goods, vehicles, a bus station or

le-praved, de-norally bad, to ion (dep-rā-vay-

adj. 1. immoral, aracter. 2. made d tastes. *ee*) *n.* (pl. -ties) edness.

yt) *v.* (dep-re-*ng*) 1. to feel and 2. to try to turn ie etc.) politely. -rē-kay-shōn) *n.* lep-rē-kā-tohr-ee) e deprecate with

shi-ayt) *v.* (de-*cl-at-ing*) 1. to r in value. 2. to de-pre-cl-a-ōn) *n.* >Do not i deprecate. li-pree-shi-ā-tohr-

rē-day-shōn) *n.* i.

to make sad, to o make less active; he stock market, to press down, de-essed' *adj.* de-

int) *n.* a substance ity of the nervous pressant *adj.* de-

-ōn) *n.* 1. a state r hopelessness, of-ptoms. 2. a long usiness and trade, employment. 3. a eric pressure, an allow on a surface. the Depression, lon, the business 1929 and ended roke out.

v) *adj.* 1. depress-al depression. de-

pressive *n.* a person suffering from mental depression.

de-priv-al (di-pri-vāl) *n.* depriving, being deprived.

dep-ri-va-tion (dep-ri-vay-shōn) *n.* 1. de-priv-al 2. a keenly felt loss.

de-priv-e (di-priv) *v.* (de-priv-ed, de-priv-ing) to take a thing away from, prevent from using or enjoying, the pri-*oner* had been deprived of food. *de-priv-ed* child, one who has been pre-vented from having a normal home life.

de-pro-gram (dec-proh-gram) *v.* (de-pro-gram-ed, de-pro-gram-ing) to restore (a person's thought processes) to normal through systematic reindoctrina-tion. de-pro-gram-er *n.*

dept. *abbr.* 1. department. 2. deponent. 3. deputy.

depth (depth) *n.* 1. being deep. 2. the dis-tance from the top down, or from the surface inward, or from front to back. 3. deep learning or thought or feeling. 4. intensity of color or darkness. 5. low-ness of pitch in a voice or sound. 6. the deepest or most central part, living in the depths of the forest. *depth* charge, a bomb that will explode under water, for use against submarines etc. In depth, with thorough and intensive investiga-tions, studied it in depth; defense in depth, a system of defense employing successive areas of resistance. out of or beyond one's depth, in water that is too deep to stand in; attempting something that is beyond one's ability.

dep-u-ta-tion (dep-yū-tay-shōn) *n.* a body of people appointed to go on a mis-sion on behalf of others.

de-pute (di-pyoot) *v.* (de-put-ed, de-put-ing) 1. to delegate (a task) to a per-son. 2. to appoint (a person) to act as one's representative.

dep-u-tize (dep-yū-tiz) *v.* (de-pu-tized, de-pu-tiz-ing) to appoint as deputy.

dep-u-ty (dep-yū-tee) *n.* (pl. -ties) 1. a person appointed to act as substitute for another. 2. a member of a legislature in certain countries, the Chamber of De-pu-ties. *deputy* sheriff, an acting sheriff.

der. *abbr.* 1. derivation. 2. derivative. 3. derived.

de-rail (dec-rayl) *v.* 1. to cause (a train) to leave the rails. 2. (of a train) to leave the rails. de-rail-ment *n.*

de-range (di-raynj) *v.* (de-ranged, de-rang-ing) 1. to throw into confusion, to disrupt. 2. to make insane. de-range-ment *n.*

der-by (dur-bee) *n.* (pl. -bles) 1. a hor-race of particular prominence. 2. a com-test of any kind open to all, o roller derby

3. (also derby hat) a man's stiff felt hat. 4. the Derby, the annual horse race at Churchill Downs, Kentucky; the annual horse race at Epsom, near London, Eng-land.

der-e-lict (der-ē-lik) *adj.* abandoned, de-serted and left to fall into ruin. derelict *n.* 1. a person who is abandoned by soci-ety or who does not fit into a normal social background. 2. an abandoned ship, car, plane, etc.

der-e-lic-tion (der-ē-lik-shōn) *n.* 1. neg-lect of duty. 2. abandoning, being aban-doned.

de-ride (di-rīd) *v.* (de-rid-ed, de-rid-ing) to laugh at scornfully, to treat with scorn.

de-ri-gueur (dē-ree-gur) required by cus-tom or etiquette, evening dress is de-ri-gueur. > French.

de-ri-sion (di-rizh-ōn) *n.* scorn, ridicule. de-ri-sive (di-rī-siv) *adj.* scornful, show-ing derision, derisive cheers. de-ri'-alve-ly *adv.*

de-ri-so-ry (di-rī-sō-ree) *adj.* 1. derisive. 2. deserving derision, too insignificant for serious consideration, o derisory offer.

deriv. *abbr.* 1. derivation. 2. derivative. 3. derived.

der-i-va-tion (der-i-vay-shōn) *n.* 1. deriv-ing. 2. origin.

de-riv-a-tive (di-riv-ā-tiv) *adj.* derived from a source. derivative *n.* a thing that is derived from another.

de-rive (di-riv) *v.* (de-ri-ved, de-riv-ing) 1. to obtain from a source, he de-rived great pleasure from music; some English words are derived from Latin, originate from Latin words. 2. to be de-scended, some English words derive from Latin. 3. to show or assert that some-thing is derived from (a source).

der-mal (dur-māl) *adj.* of the skin.

der-ma-ti-tis (dur-mā-trī-tis) *n.* inflam-mation of the skin.

der-ma-tol-o-gist (dur-mā-tol-ō-jist) *n.* a specialist in dermatology.

der-ma-tol-o-gy (dur-mā-tol-ō-jee) *n.* the scientific study of the skin and its diseases.

der-mis (dur-mis) *n.* skin, the layer of tis-sue below the epidermis.

de-ro-gate (der-ō-gayt) *v.* (de-ro-gat-ed, de-ro-gat-ing) to detract from, your statement derogates my authority.

de-ro-ga-tion (der-ō-gay-shōn) *n.*

de-ro-g-a-to-ry (di-ro-g-ā-tohr-ee) *adj.* disparaging, contemptuous.

der-ick (der-ik) *n.* 1. a kind of crane with an arm pivoted to the base of a central post or to a floor. 2. a framework over an oil well or other drilled hole, holding the drilling machinery etc.

derelict / desecrate

der-ri-ère (der-i-air) *n.* buttocks. > French.

der-ring-do (der-ing-doo) *n.* heroic cour-age or action.

der-rin-ger (der-in-jēr) *n.* a small large-bore pistol. > From its American inven-tor, Henry Deringer.

der-ris (der-is) *n.* 1. an East Indian legu-minous plant. 2. an insecticide made from its powdered root.

der-vish (dur-vish) *n.* a member of a Mus-lim religious order, vowed to poverty and chastity.

de-sal-i-nate (dec-sal-i-nayt) *v.* (de-sal-i-nat-ed, de-sal-i-nat-ing) to desalt. de-sal-i-na-tion (dec-sal-i-nay-shōn) *n.*

de-sa-lin-ize (dec-sal-i-niz) to desalt. de-sal-i-ni-za-tion (dec-sal-i-ni-zay-shōn) *n.*

de-salt (dec-sawlt) *v.* to remove salt from (especially seawater).

de-scale (dec-skayl) *v.* (de-scaled, de-scal-ing) to remove scale from (a kettle or boiler etc.).

des-cant (des-kant) *n.* a melody sung or played in accompaniment to the main melody.

de-s-cend (di-send) *v.* 1. to come or go down. 2. to slope downward. 3. to make a sudden attack or visit, the whole family descended on us for Easter. 4. to sink or stoop to unworthy behavior, to lower oneself, they would never descend to cheating. 5. to be passed down by inheri-tance, the title descended to his son.

de-s-cend-ant (di-sen-dānt) *n.* a person who is descended from another, the descendants of John Adams include many famous Americans.

de-s-cent (di-sent) *n.* 1. descending. 2. a way by which one may descend. 3. a downward slope. 4. a sudden attack or invasion, the Danes made descents upon the English coast. 5. lineage, family ori-gin, they are of French descent.

de-scribe (di-skrīb) *v.* (de-scribed, de-acrib-ing) 1. to set forth in words, to say what something is like. 2. to mark out or draw the outline of, to move in a certain pattern, described o complete circle. des-crib'a-ble *adj.*

de-scrip-tion (di-skrīp-shōn) *n.* 1. de-scribing. 2. an account or picture in words. 3. a kind or class of thing, there's no food of any description.

de-scrip-tive (di-skrīp-tiv) *adj.* giving a description.

de-s-cry (di-skrī) *v.* (de-scried, de-scry-ing) to catch sight of. > Do not confuse *descry* with *decry*.

des-e-crate (des-ē-krayt) *v.* (des-e-crāt-ed, des-e-crāt-ing) to treat (a